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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/205,096	12/03/1998	DANIEL B. DRACHMAN	01107.77737	8208

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	28

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/205,096	DRACHMAN, DANIEL B.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,42,46,48-51,53,55-57,59 and 64-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,42,46,48-51,53,55-57,59 and 64-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment and response filed 3/4/03 has been entered as Paper No. 27. Claims 43-45, 47, 52, 54, 58, 60-62 have been cancelled; and claims 41, 46, 48, 51, 53, 55, 59, 63, 64, 66, and 67 have been amended. Currently, claims 41, 42, 46, 48-51, 53, 55-57, 59, and 63-67 are pending and under examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the response and amendment to pending claims will not be reiterated. The arguments in paper #27 would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

Claims 42, 55-57, 59, 63, 64, and 67 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In paper #27, the applicant argue that the genus of the structures that being functional located with respect to the auto-antigen or portion thereof was known before the filing of the instant application and submitted Exhibits A-F to show the teachings for a polynucleotide encoding a polypeptide comprising a peptide of interest functionally linked to a signal peptide and transmembrane/cytoplasmic tail.

The argument and Exhibits have been fully considered but they are not persuasive with regard to supporting the full scope of the claims.

The claims encompass a genus of structures that encompass any signal sequence linked to a transmembrane/cytoplasmic tail, however, the specification and four of the six Exhibits (A, B, D, E) only disclose the LAMP family proteins that promote protein endosomal processing. Exhibit C teaches a signal protein that promote trans Golgi network targeting, not endosomal processing as required by the claims; and Exhibit F disclosed a protein GP75, which target to melanosomal membrane.

An adequate written description for the genus of signal sequences requires more than a mere statement that it is part of the invention; what is required is a description of the chemical structures of the protein itself. It is not sufficient to define the agents solely by its principal biological property, i.e. "facilitate the auto-antigen's endosomal processing", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any peptide with that biological property. Also, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all signal peptides that achieve a result without defining what means will do is not in compliance

with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical and physical properties or sequences of the genus of signal peptides, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because LAMP alone does not provide adequate written description for the genus of structures encompassing any signal peptide that facilitate the auto-antigen's endosomal processing. Therefore, only the described LAMP peptides meet the written description provision of 35 U.S.C. §112, first paragraph.

ENABLEMENT REQUIREMENT

Claims 42, 55-57, 59, 63, 64, and 67 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As discussed in above, since the specification fails to teach the genus of the structures that encompass any signal sequence, accordingly, except the described LAMP signal sequences, the skilled in the art would not know how to practice the invention without undue experimentation.

Therefore, the rejection stands.

Claims 41, 42, 46, 48-51, and 53 stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for

ablation of autoreactive T cells in *any* and *all* auto-immune disease patients using *any* and *all* antigen-presenting cells, *any* and *all* viral vectors, *any* and *all* signal sequences, *any* and *all* auto-antigens; and it does not reasonably provide enablement for *selective* ablation of auto-antigen-specific T cells in *any* auto-immune disease patient using *Fas-L*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In paper #27, applicants argue that the claims do not require ablation of auto-antigen-specific T cells over a particular period of time following administration, e.g. beyond eight days, and that the Office has not present evidence or sound scientific reasoning to doubt that the HA-receptor bearing T cells are activated.

The arguments have been fully considered but they are not persuasive because as indicated previously, the claims are given the broadest reasonable interpretation *in light of the specification*, as such the claims clearly read on a therapeutic method for treating any and all autoimmune diseases in a patient. Accordingly, the claims are evaluated by that standard. Thus, in the context of treating autoimmune disease, the deletion of auto-reactive T cells for eight days (Shown in a post-filing declaration) is not sufficient for treating an on-going autoimmune disease.

A simple comparison of the claims and the supporting data would find discrepancy between the scope of the claims and guidance provided. The instant invention claims methods of treating patients suffering with an autoimmune disorder by introducing a gene encoding the entire auto-antigen or portion of the auto-antigen and a

FasL, and re-introducing the APCs in vivo so as to activate and ablate the auto-antigen-specific T cells using any route of administration, any antigen presenting cells, any auto-antigen, linked to any signal sequence, with any viral vectors.

The specification only provides *in vitro* experimental data to illustrate the claimed method, and fails to show any detrimental effect on activated auto-reactive T cells by any product in vivo. The post-filing Declaration is insufficient to support the scope of the claim because the experiment was conducted in a transgenic animal whose T cells have been genetically modified such that they are not comparable with a patient suffering a spontaneous occurring autoimmune disease, where many genetic, acquired, and environmental factors acting in concert to trigger and sustain an autoimmune response. Further, the HA-receptor transgenic mouse is not an autoimmune disease model.

Based on the teachings in the art (Deonarain, Verma et al, and Crystal et al) and analysis of the experiment disclosed in the post-filing declaration (current Exhibit H), the Office provided scientific reasoning for placing reasonable doubt on whether the Declaration is sufficient to support the scope of the claims. For example, the ablation of the T cells is short-lived and not strictly selective.

The non-selective killing effect seen in the transgenic animal appeared to be associated with the presence of FasL, which receptor may be present in even non-activated T cells. Such non-activation-specific targeting effect may be seen in the control group of the transgenic mouse study on day 5 and 8 after the administration of tranfected APCs, wherein even absent of a specific (HA) antigen, the percentage of HA-

receptor bearing T cells decreased (results in Table 1 of Appendix 18). The short-lived ablation may be also seen in the instant transgenic mouse study, wherein although on day 2 after transduced APCs administration, HA-receptor bearing T cells are significantly decreased to 10% of the control, they recovered to 50% of the control on day 8, thus, the ablation of antigen-specific T cells has not been sufficiently enabled even in these transgenic mice. Moreover, the Declaration and the specification fail to teach whether any therapeutic effect can be achieved by the degree of the decrease in the numbers of auto-reactive T cells, and it is highly likely that the remain autoreactive T cells are sufficient to sustain the autoimmune disease, particularly considering the constant presence of APCs expressing the auto-antigen. The Declaration only used introperitoneal injection of VVV transfected APCs, whereas the claims encompass any route of administration using any vector. Accordingly, the specification and the Declaration fail to support the full scope of the claims.

Applicant submitted Exhibits I-Q to show that the skilled in the art knows how to prepare the antigen presenting cells. However, preparing and transferred the transduced APCs are the relatively straightforward and easy steps in the claimed method. The real challenge is the selection of the right auto-antigens, eliciting the right immune response, and selective functioning of the FasL *in vivo* on the auto-reactive, not the regulative T lymphocytes, other immune cells, and other innocent host cells. It is because of this concern, the Office action cited the teaching of *Von Herrath et al* (Ann Med 2000 Jul;32:285-92). *Von Herrath et al* extensively teach the presence of two types of T cells in an autoimmune disease, autoaggressive and regulative, why it is difficult to

selectively induce the desired type of T cells (pages 277-288), the presence of different types of "auto-antigen" which could induce autoaggressive or regulative responses, and the changing role of the "auto-antigen" in different stages of an autoimmune process such as diabetes (table 2, text in left column, page 289). Applicants submitted Exhibits R-T to show that auto-antigens for which auto-aggressive T cells are specific were known in the art before the effective filing date. However, in the references, the authors did not identify whether those antigens are autoaggressive or regulative. Further, these few auto-antigens are not sufficient to support the full scope of the claims that encompass any of various autoimmune diseases. *Von Herrath et al* also teach general issues that need to be addressed before gene therapy could be used for inducing tolerance in autoimmune diseases in clinic (the Section bridging pages 289-290). The issues, although general, apply to the quest of enablement of instantly claimed process because it illustrated the state of the art related to the in vivo use of the exogenous DNA vector, the risk of spontaneous mutation, the host immune response to the exogenous DNA and expressed protein, and the persisting effects of the exogenous gene, which particular is a concern when a detrimental product is administered in vivo, because FasL could non-selectively triggers death of cells other than auto-reactive T cells.

With respect to the signaling sequences, the applicant argues that it is predictable to use LAMP-1 protein. However, as indicated earlier, the claims embrace a genus of signal sequences, which are not limited by the LAMP-1 protein.

With respect to the vectors and routes of administration, applicant argues that *Makrides and Robbins* teach factors to be considered, one of skill in the art would have

been able to select such a vector. Applicant is reminded that the teachings of *Makrides and Robbins* were published in a post-filing date, and at the post-filing date, the issues are remain, it retrospectively illustrated the state of the art at the time of the filing.

In paper #27, applicant argues that the teaching of *Von Herrath* does not apply because *Von Herrath* refers to DNA vaccine delivery, not delivery of APCs. This is not found persuasive because the *Von Herrath* teaching is not cited as prior art, but gene therapy for autoimmune disease in general. The claims encompass delivery of a DNA vector encoding FasL, thus, the citation applies properly.

As to the relevance of the teaching of *Kristiansen et al* (Genes and Immunity 2000;1:170-84), it was cited to illustrate the importance of timing of administration, whether it is the antigen or the factor working on ablating the reactive T cells. In addition to the passage cited, *Kristiansen et al* showed that given the CTLA4 at different stage of the diseases would produce different effects (table 1).

With respect to the fate of the antigen presenting cells and viral vectors, the concern of the Office is further supported by *von Herrath et al*, who teach that repeated exposure to the autoantigen would induce memory lymphocytes that can then respond much more rapidly to the same antigen resulting in *hyperimmunity*, "A MOST UNDESIRABLE EFFECT, IF IT INVOLVES AUTOAGGRESSIVE MEMEORY LYMPHOCYTES" (left column, page 288). And persistent presence of FasL would not only interact with the autoreactive or regulative T cells but also any cell in the host that bear Fas receptor, and induce unwanted cell death.

With respect to the teaching of *Carrieri et al,* (Ann Med 1999;31:52-6), the applicant argues that the teaching does not change the fact that APC expressing an antigen will activate T cells, and FasL would then ablate the activated T cells. The argument is not persuasive because the claimed invention is evaluated by the standard of treating autoimmune disease, not whether it could ablate activated T cells. The Carrieri reference was cited to illustrate the complexicity of autoimmune diseases, i.e. the presence of autoaggressive T cells is caused by combination factors such as the constant presence of over-expressed auto-antigen in thymus, defective regulation of apoptosis, and the defects either in the number or function of CD8+ T cells (table 1, *Carrieri et al,* Ann Med 1999;31:52-6). Accordingly, even some of the T cells may be ablated, it is unpredictable whether this is sufficient in preventing and treating any and all autoimmune diseases. In general, the specification and the Declaration fail to teach an overall therapeutic effect of administrating transduced APCs on any autoimmune disease particularly when taking into account of the host factors, let alone any and all autoimmune diseases.

With respect to the argument that the Declaration demonstrates a simple principle that can be applied to any antigen, including auto-antigens, thus, it is sufficient to support the broad claims. Assuming the post-filing experimentation illustrates a case of treating a type of autoimmune disease, it is noted that in applications directed to inventions in arts where the results are unpredictable such as treatment of any and all autoimmune diseases, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA

1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Goodman, 29 USPQ2d 2010 (CA FC 1993); In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT." Considering the distinct mechanism of pathogenesis in various autoimmune disorders, it is unpredictable from the disclosure whether the instant method would function as claimed.

The Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material or **of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate

enablement.Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

The circumstance stated in the court decision is amenable to the instant application, wherein there is little disclosure of any conditions, which the claimed process can be carried out. Repeatedly in the response, applicant simply asserts that every related factor concerning the practice of the broadly claimed invention is within the skilled of the art. Applicant is reminded that it is the specification, not the knowledge of the skilled in the relevant art that must provide the novel aspects of claimed invention.

Applicant is remained that the court has concluded that "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC" *(In re Marzocchi and Horton, 169 USPQ 367 CCPA1971)*. When instant claims read on a method for the treatment of any and all autoimmune diseases with little data as support, a doubt is reasonable since there is no universal cure for the disease as of today. Furthermore, the Office has provided numerous teachings to illustrate the state of the art and the levels of those skilled artisans to indicate the doubt is reasonable. Thus, it is applicants' duty to provide sufficient teaching to enable the claimed invention.

For the reasons of record and those set forth above, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The prior rejection of claims 54, 58, 59, 60, and 64 under 35 U.S.C. 103(a) as being unpatentable by *August et al* (US 5,633,234) is withdrawn in view of the amendment.

The prior rejection of claims 58, 59, and 64 under 35 U.S.C. 102(e) as being anticipated by *Steinman et al* (US 6,300,090) is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 54, 55, 56, 58, 60, 61, 62, 66, and 67 under 35 U.S.C. 103(a) as being unpatentable over *August et al* (US 5,633,234), *Attassi et al,*(Cri

Rev 1997;17:481-95), and further in view of *Bellgrau et al* (US 5,759,536) now applies to the amended claims 55, 56, and 66.

Claims are directed to antigen presenting cells transfected with a polynucleotide encoding a protein comprising an auto-antigen or fragment thereof, functionally linked to a signal peptide and a transmembrane/cytoplasmic tail and further transduced with a polynucleotide encoding a FasL.

August et al teach transfecting an APC with an auto-antigen of interest linked to an endosomal targeting signal to induce anergy of T cells in autoimmune diseases, e.g. *myasthenia gravis* (column 19, lines 41-54), *August et al* do not teach transfecting APCs with FasL or the particular extracellular domain of α-subunit of AchR.

Attassi et al teach that in MG disease, the extracellular portion of AchR α subunit serves as epitope recognized by the T and B lymphocytes (see abstract and right column in page 482).

Bellgrau et al teach use of Fas Ligand to suppress T lymphocyte-mediated immune response. They teach that cells expressing an autoantigen could be further introduced to a gene expressing Fas ligand, so that suppress T lymphocyte-mediated disease (see claims 6 and 7). They go on to teach that the cells could be used in transplant rejection, in autoimmune diabetes, and *myasthenia gravis* (column 5, lines 23-40). *Bellgrau et al* do not particularly teach an antigen presenting cell.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *August et al, Attassi et al, and Bellgrau et al,* by simply including the FasL coding region in the viral vector of *August et*

al, or using two separate means delivering the autoantigen and the FasL as taught by *Bellgrau et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because the combined effect would be more effective in reducing autoreactive T cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In paper #27, the applicant argues that August teaches not to active T cells whereas Bellgrau teaches suppress activated T cells, one of skill in the art would not have been motivated to include a molecule that kills activated T cells.

The argument is not persuasive because both references teach different means of reducing autoreactive T cells in the context of managing autoimmune diseases, either by not activating new auto-reactive T cells or by killing of the existing harmful T cells. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art compositions of cells transfected with expression vectors encoding autoantigens and FasL-all taught to be useful for the treatment of autoimmune diseases, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of an autoimmune disease with a reasonable expectation of success.

Conclusion

No claim is allowed. Claims 57, 59, 63, 64, and 67 appear to be free of cited art of record, however, they are subject to other rejections.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
May 15, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER